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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MICHAEL E. GARST

Appeal 2009-006222[1]
Application 09/903,954
Technology Center 1600

Decided: January 11, 2010

Before ERIC GRIMES, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to methods of treating degeneration of the optic nerve. The Examiner rejected the claims as obvious.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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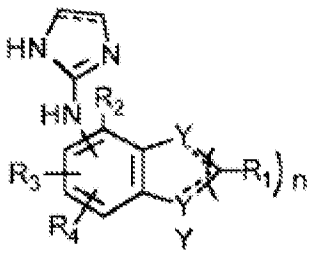
[1] Allergan, Inc. is the real party in interest.

STATEMENT OF THE CASE

Claims 21-25 and 27 are pending and on appeal (App. Br. 5).[2] Claim 21 is representative[3] and reads as follows:

> 21) A method of treating degeneration of the optic nerve and the retinal ganglion cells of a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



formula (I)

> wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R1; R1 is hydrogen, lower alkyl or oxo; R2, R3 and R4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=l, and their pharmaceutically acceptable salts and esters as appropriate.

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[2] Appeal Brief filed January 25, 2007.

[3] Appellant filed an after-final amendment which, among things, deleted the recitation "and the retinal ganglion cells" from the preamble of claim 21 (App. Br. 6, *see also* Amendment After Notice of Appeal, p. 2 (entered July 10, 2006)). While the Examiner has not considered this amendment, our consideration of the appealed rejection is not affected by the amendment. Therefore, in the interest of compact prosecution, we will decide the appeal rather than remand the case to Examiner to consider the amendment.

The Examiner cites the following documents as evidence of unpatentability:

Woodward	US 5,877,211	Mar. 2, 1999

Rochelle Nataloni, *LASIK study shows brimonidine provides neuroprotective effect*, 17 OCULAR SURG. NEWS 28 (1999) (hereinafter "Yavitz").[4]

The sole rejection before us for review is the Examiner's rejection of claims 21-25 and 27 under 35 U.S.C. 103(a) as being obvious over Yavitz and Woodward (Ans. 3-4).

OBVIOUSNESS

ISSUE

The Examiner finds that "Yavitz teaches the use of the claimed compound, brimonidine, being an alpha adrenergic agonist, having neuroprotective effect during ophthalmic surgery" (Ans. 3). The Examiner concedes that Yavitz "differs from the claimed invention in the presence of a prostaglandin receptor agonist" (*id.* at 3-4).

The Examiner nonetheless concludes that an ordinary artisan would have considered it obvious "to add a prostaglandin to the composition of Yavitz, considering that Woodward teaches the neuroprotective effect of prostaglandin receptor agonists in [the] ophthalmic field" (*id.* at 4). The Examiner reasons that the artisan would have been prompted to combine the teachings of Yavitz and Woodward "since one relates to the use of the

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[4] While the cited article reports on a study by Dr. Yavitz, it appears to be authored by Rochelle Nataloni. Nonetheless, both Appellant and the Examiner refer to the article as "Yavitz," and we do the same for convenience.

claimed alpha-adrenergic agent having neuroprotective activity in the ophthalmic field and the other relates to the use [of] prostaglandins having neuroprotective effect in the ophthalmic field" (*id.*).

Appellant argues each of the rejected claims separately, contending that the Examiner failed to make a prima facie case of obviousness, for a variety of reasons (App. Br. 9-17).

In view of the positions advanced by Appellant and the Examiner, the issue with respect to this rejection is whether Appellant has shown that the Examiner failed to make a prima facie case that an ordinary artisan would have considered claims 21-25 and 27 obvious in view of Yavitz and Woodward.

FINDINGS OF FACT ("FF")

1. Yavitz discloses that a "small double-masked study showed almost universal nerve fiber layer thinning after laser in situ keratomileusis (LASIK). Further, the study showed that the nerve fiber thinning was mitigated or totally prevented by brimonidine" (Yavitz 28).

2. Yavitz discloses that the "further implication in [t]his finding . . . is that for one of the first times, it has been demonstrated on a limited basis that brimonidine is neuroprotective" (*id.*).

> "Neuroprotectivity is a hot topic and it has never been proven in a human before. It has been shown in rat eye studies, but never in human eyes. So the major implication of this is not in refractive surgery at all, but in the fact that if [brimonidine] indeed shows neuroprotection, it becomes the premier glaucoma drop, at least until another drop shows the same kind of neuroprotectivity," Dr. Yavitz told OCULAR SURGERY NEWS.

(*Id.*)

3. Woodward discloses "the use of EP_2 receptor agonists to provide a neuroprotective effect to the eye of a mammal" (Woodward, col. 1, ll. 6-8).

4. Woodward discloses that glaucoma "is a disease of the eye characterized by increased intraocular pressure" (*id.* at col. 1, ll. 16-17).

5. Woodward discloses:

> It has long been known that one of the sequelae of glaucoma is damage to the optic nerve head. This damage, referred to as "cupping", results in depressions in areas of the nerve fiber of the optic disk. Loss of sight from this cupping is progressive and can lead to blindness if the condition is not treated effectively.

(*Id.* at col. 1, ll. 54-59.)

6. According to Woodward, the prior art recognized that "some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma" (*id.* at col. 2, ll. 65-67).

7. Woodward discloses that, among useful prior art prostaglandins, "in particular PGE_2 and $PGF_{2\alpha}$ and the C_1 to C_5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in glaucoma management" (*id.* at col. 3, ll. 10-14).

8. Woodward discloses that the "isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, which was attributed to its more effective penetration through the cornea. In 1987 this compound was described as 'the most potent ocular hypotensive agent ever reported'" (*id.* at col. 3, ll. 19-24 (citations omitted)).

9. Woodward discloses, however, that certain side effects greatly limit the "clinical potential of prostaglandins in the management of conditions

associated with increased ocular pressure, e.g. glaucoma" (*id.* at col. 3, ll. 31-33).

10. According to Woodward, the prior art discloses certain "prostaglandin esters with increased ocular hypotensive activity accompanied by no or substantially reduced side-effects," including "11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$," as well as "15-acyl prostaglandins" and "11,15- 9,15- and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$" (*id.* at col. 3, ll. 40-50).

11. In light of these prior art teachings, Woodward discloses that "EP_2-receptor agonists are potent neuroprotective agents. We have further found that (±) trans-2-[-4(1-hydroxyhexyl)phenyl]-5-oxocyclopentaneheptanoicacid, and certain other EP_2-receptor agonists, described below, and ester and unsaturated derivatives thereof, are especially useful in providing a neuroprotective effect to the eye of a mammal, e.g. a human" (*id.* at col. 3, l. 66, through col. 4, l 5).

12. Woodward measured the neuroprotective effect of test compounds by exposing cultured rat hippocampal neuron cells to the excitatory amino acid NMDA along with the test compounds, and using the amount of lactate dehydrogenase (LDH) activity released from the cells as a measure of cytotoxicity or neuron injury (*id.* at col. 7, l. 65 through col. 8, l. 44).

13. Woodward presents the results of its experiments in Figures 1A through 1D, which "show a comparison of the neuroprotective effects of EP_2 agonists, e.g. see FIGS 1C and 1D, with prostaglandins having no EP_2 agonist activity, e.g. see FIGS 1A and 1B, in preventing neuronal damage" (*id.* at col. 4, ll. 58-61).

Figures 1C and 1D are reproduced below:

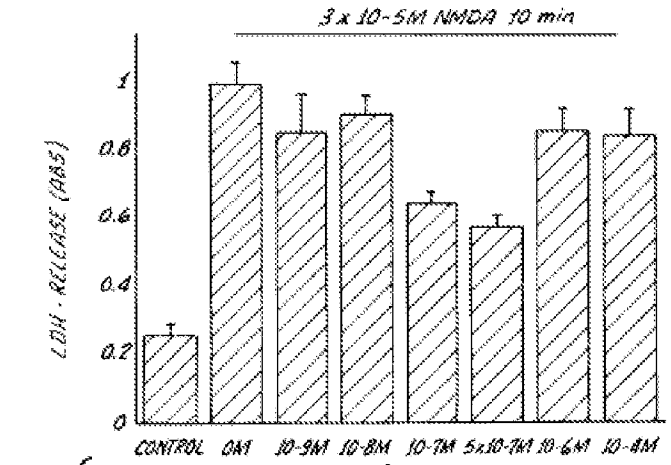

FIG. 1C.

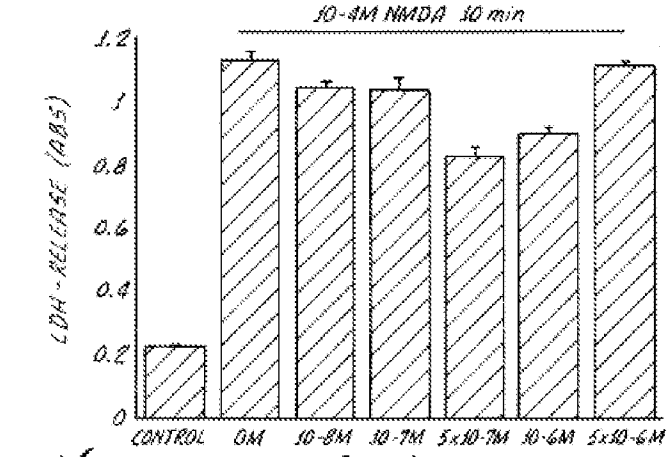

FIG. 1D.

Figures 1C and 1D show, respectively, the effect of treatment of cultured neurons with different concentrations of test compound AH 13205 and PGE_2, measured as the amount of LDH released from the treated cells. As can be seen, both AH 13205 and PGE_2, the agonist of the EP_2 receptor, reduce the amount of LDH released compared to cells without added AH 13205 or PGE_2 ("0M").

14. Figures 1A and 1B of Woodward are reproduced below:

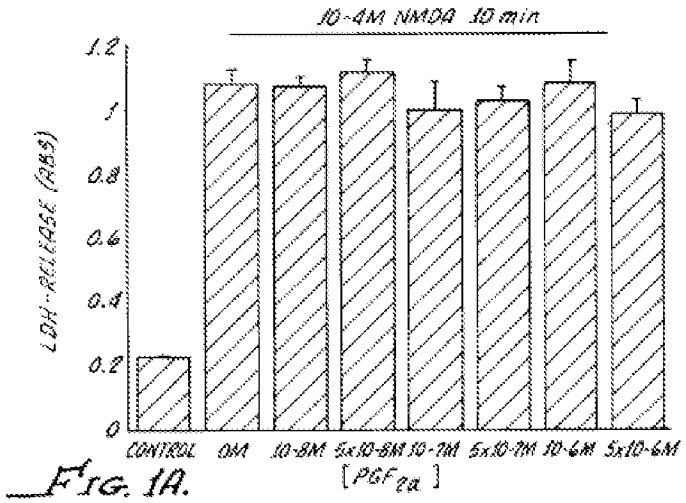

FIG. 1A.

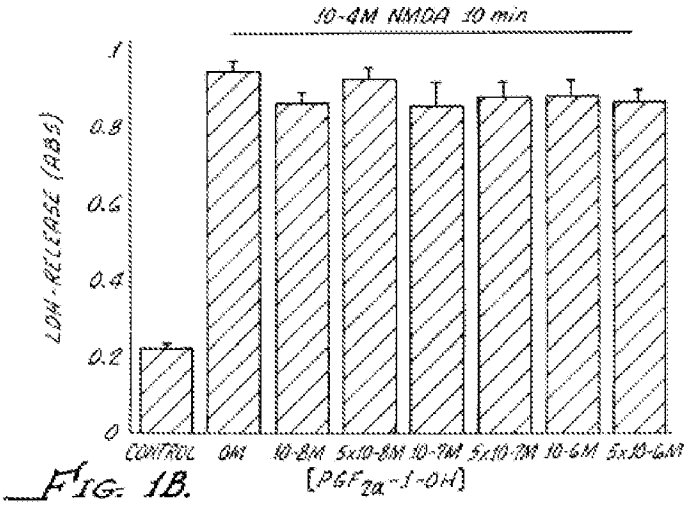

FIG. 1B.

Figures 1A and 1B show, respectively, the effect of treatment of cultured neurons with different concentrations of $PGF_{2\alpha}$ and $PGF_{2\alpha}$1-OH, measured as the amount of LDH released from the treated cells. As can be seen, neither compound appears to significantly affect the release of LDH from NMDA-treated cells.

15. Woodward interprets these results by stating that "$PGF_{2\alpha}$ and $PGF_{2\alpha}$ 1-OH are inactive, thereby indicating that this is a specific EP_2 receptor mediated effect" (*id.* at col. 8, ll. 49-51).

PRINCIPLES OF LAW

In *KSR Int' l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court addressed the question of obviousness, and ultimately reaffirmed that "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)).

The Court reasoned that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.*

As our reviewing court has pointed out, when evaluating claims for obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986).

Accordingly, "'[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" *Id.* (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)).

Thus, "in a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck &*

Co., Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

Also, it is well settled that "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

ANALYSIS

Appellant's arguments do not persuade us that the Examiner failed to make a prima facie case that an ordinary artisan would have considered claims 21-25 and 27 obvious in view of Yavitz and Woodward.

Claim 21 recites treating optic nerve degeneration by administering to a mammalian subject "a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I) . . . and their pharmaceutically acceptable salts and esters as appropriate." It is undisputed that formula (I) encompasses brimonidine.

As the Examiner points out, Yavitz teaches that brimonidine likely has neuroprotective properties, which would make it a useful treatment for glaucoma (FF 1, 2). Yavitz does not appear to disclose combining brimonidine with other drugs, such as prostaglandins, to treat glaucoma.

Woodward, however, discloses that optic nerve damage is one of the symptoms and consequences of glaucoma (FF 5), and that "some prostaglandins are highly effective ocular hypotensive agents and are ideally suited for the long-term medical management of glaucoma" (FF 6). We agree with the Examiner that an ordinary artisan, informed by the references that brimonidine and prostaglandins were useful in treating glaucoma, would

have considered it obvious to use both of those agents to treat glaucoma, and its concomitant optic nerve degeneration.

Appellant urges that this conclusion is erroneous, because, although "Woodward discusses the use of EP2 agonists to treat ocular nerve damage, not all such agonist compounds are themselves prostaglandins" (App. Br. 10). Moreover, Appellant argues

> Woodward teaches away from the use of "prostaglandins" generally as neuroprotectants, since prostaglandin PGF2α and other prostaglandin FP2α receptor agonists are said to be "inactive". The term "neuroprotection" in Woodward, as evidenced by e.g., claim 1 of the '211 patent, appears to be construed to exclude any neuroprotective benefits attendant to lowering IOP (and thus avoiding a mechanical crushing injury to retinal neurons). That the person of ordinary skill in the art would so adopt this interpretation is a reasonable assumption from a reading the text of Woodward, since prostaglandin F2α, a potent ocular hypotensive, is said not to be active. '211 patent, column 8, lines 49-51.

(*Id.*)

We are not persuaded by these arguments. It might be true that not all EP_2 receptor agonists are prostaglandins. However, Woodward discloses that PGE_2, an EP_2 receptor agonist and one of the prostaglandins recited in Appellant's claims, not only was recognized in the art as having ocular hypotensive activity recommending its use in treating glaucoma (FF 7), but also had an EP_2 receptor-mediated neuroprotective effect comparable to other therapeutically active compounds tested by Woodward (FF 13).

Thus, in view of Woodward's teaching that EP_2 receptor agonists were useful in treating glaucoma due to their neuroprotective effects (FF 3, 11), we agree with the Examiner that an ordinary artisan would have been

prompted to combine prostaglandin agonists of that receptor, such as PGE_2, with other glaucoma-treating agents, like brimonidine, to treat glaucoma and its attendant optic nerve damage.

We are not persuaded that Yavitz fails to suggest using brimonidine in such methods. We note, as Appellant argues, that Yavitz's conclusions are based on a small study relating to the optic nerve crush injury caused by raising intraocular pressure during LASIK surgery (FF 1). However, Yavitz affirmatively states that its findings suggest a neuroprotective effect for brimonidine that would make it suitable for treating glaucoma patients (FF 2).

As noted above, "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-04.

In the instant case Yavitz directly discloses the therapeutic agent, brimonidine, as well as the target disorder, glaucoma and the nerve damage that accompanies it (FF 2). Thus, Yavitz does much more than merely provide the ordinary artisan with numerous possible choices for treatment plans or a broad promising field with only general guidance for a solution. *Cf. O'Farrell*, 853 F.2d at 903.

In sum, Appellant's arguments do not persuade us that the Examiner failed to make a prima facie case of obviousness with respect to claim 21. Accordingly, we affirm the Examiner's rejection of that claim as being obvious in view of Yavitz and Woodward.

Claim 22 recites "[t]he method of claim 21 wherein the prostaglandin is selected from the group consisting of PGF2α, PGE2 . . . and their

pharmaceutically acceptable esters and salts, as appropriate." Thus, PGE_2 is among the numerous compounds listed in claim 22 which may be combined with brimonidine.

As noted above, Woodward discloses that PGE_2 meets two criteria for being useful in treating glaucoma. First, it has ocular hypotensive activity (FF 7), and second, it has a neuroprotective effect (FF 13). Appellant's arguments therefore do not persuade us that the Examiner erred in finding that an ordinary artisan would have been prompted to treat glaucoma, and its concomitant optic nerve degeneration, with both PGE_2 and brimonidine. We accordingly affirm the Examiner's rejection of claim 22 as being obvious in view of Yavitz and Woodward.

Claim 23 depends from claim 22, and limits the prostaglandin to, among others, PGF2α-11-pivalyl ester and PGF2α1-isopropyl ester. We note, as Appellant argues, that Woodward discloses that "$PGF_{2\alpha}$ and $PGF_{2\alpha}$ 1-OH are inactive" in its test for neuroprotective activity, which shows that those compounds do not have the EP_2 receptor-mediated activity described by Woodward (FF 16).

Woodward also discloses, however, that the 11-pivaloyl[5] and isopropyl esters of $PGF_{2\alpha}$ were known in the art to be useful for treating glaucoma (FF 7, 8, 10). Thus, while it may be true that claim 23 recites prostaglandin derivatives which are not preferred by Woodward for treating glaucoma, Woodward does in fact disclose that those compounds were recognized in the art for treating that disorder.

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[5] Appellant does not dispute that Woodward's "11-pivaloyl" ester is the same as the "11-pivalyl" ester recited in claim 23.

We are therefore not persuaded that the Examiner erred in finding that an ordinary artisan would have been prompted to treat glaucoma, and its concomitant optic nerve degeneration, with a prostaglandin derivative encompassed by claim 23 and brimonidine. We accordingly affirm the Examiner's rejection of claim 23 as being obvious in view of Yavitz and Woodward.

Claim 24 depends from claim 21[6], and limits the alpha adrenergic agent recited in claim 21 to those encompassed by the formula (II) recited in claim 24.[7] Appellant does not dispute that formula (II) encompasses brimonidine. As we agree with the Examiner that Yavitz and Woodward would have prompted an ordinary artisan to treat glaucoma, and its attendant optic nerve degeneration, with both brimonidine and a prostaglandin, we affirm this rejection as well.

Claim 25 depends from claim 23 limits the alpha adrenergic agent to brimonidine. We therefore also affirm this rejection, for the reasons discussed above.

Claim 27 depends from claim 21, and limits the prostaglandin to the 11-pivalyl ester of PGF2α, and the alpha adrenergic agent to brimonidine. As discussed above, while the 11-pivaloyl ester of $PGF_{2\alpha}$ does not appear to be among Woodward's preferred neuroprotective agents, Woodward

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[6] In addition to reciting dependency from claim 21, claim 24 also recites that "all other variables [in formula II] are defined as in claim 14." As Appellant points out, claim 14 has been canceled. We therefore treat claim 24 as if it depended from claim 21.

[7] It appears that the image of formula (II) was lost when the claims were copied into the Appeal Brief (*see* App. Br. 21). The formula can be seen in the copy of the claims entered into the electronic filewrapper on January 9, 2006, however.

nonetheless discloses that that prostaglandin derivative is in fact useful for treating glaucoma (FF 10).

We are therefore not persuaded that Woodward teaches away from using the 11-pivaloyl ester of $PGF_{2\alpha}$ to treat glaucoma. Nor do we agree that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to treat glaucoma, and its concomitant optic nerve degeneration, with both the 11-pivaloyl ester of $PGF_{2\alpha}$, and brimonidine, given the disclosures of Yavitz and Woodward as discussed above. We therefore affirm the Examiner's rejection of claim 27 as being obvious over those references.

SUMMARY

We affirm the Examiner's rejection of claims 21-25 and 27 under 35 U.S.C. 103(a) as being obvious over Yavitz and Woodward.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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